



UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/304, 147 09/12/94 ROBERTS

1 9101BCIP
EXAMINER

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18N2/0628

ART UNIT

PAPER NUMBER

5

1811
DATE MAILED:

06/28/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on 12/15/94 This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s); 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892. *1 page*
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449. *9 pages*
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474..
6. _____

Part II SUMMARY OF ACTION

1. Claims 1 - 9 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. Claims _____ have been cancelled.
3. Claims _____ are allowed.
4. Claims 1 - 9 are rejected.
5. Claims _____ are objected to.
6. Claims _____ are subject to restriction or election requirement.
7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. Formal drawings are required in response to this Office action.
9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).
11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).
12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.
13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. Other *The drawings have been approved*

EXAMINER'S ACTION

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The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1811.

The preliminary amendment and declaration filed 12/5/94 are acknowledged. Claims 1-9 are now pending in the application.

All references listed on PTO-1449 are not provided in this application, except for the two U.S. Patents, namely, Patent Nos. 4,376,110 and 4,486,530. However, the reference cited in PTO-1449, except for the two have been previously considered on parent application Serial No. 07/715,419 and made of record therein. Hence, all the references cited in PTO-1449 in the instant application have been considered and signed.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-9 are rejected under 35 USC 103 as being unpatentable over Morrow et al., (Analytical Biochemistry, Volume 184, pp. 1-10, January 1990).

The instantly claimed invention is directed to a method of determining oxidative stress in vivo by quantification of prostaglandin-like compounds and their metabolites produced by a noncyclooxygenase free radical catalyzed mechanism in either biological fluid or tissue and a composition thereof.

Morrow et al. disclose the discovery that prostaglandin F₂-like (PGF₂) compounds can be found readily by a noncyclooxygenase

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oxidative mechanism involving plasma lipids which leads to the formation of four regioisomers of PGF₂, each of which can theoretically be composed of a mixture of eight racemic diastereomers (See Figure 5). The reference also discloses an assay system based upon detection of multiple PGF₂ compounds with levels ranging from approximately 5 to 40 pg/m.

Morrow et al. differ from claims 1-9 in failing to teach a method of determining the oxidative stress in vivo. However, it would be obvious to select and use any known method of interest for the intended purpose of determining oxidative stress in vivo. Based on in vitro experimentation (investigative data), one of ordinary skill in the art would develop an art recognized animal model and correlate to human utility for potential therapeutic agent which eventually intended for human application. Therefore, one of ordinary skill in the art would have been motivated to develop or use the already established in vitro data of Morrow et al. for the in vivo efficacy of the instantly claimed invention.

Moreover, the instant method, which fall within the scope of the prior art method and composition would have been prima facie obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made because in the absence of sufficient evidence to the contrary, Applicants claims are directed to optimization of an "art recognized variable" which is well within the purview of one of ordinary

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skill in the art In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). Also, the selection of the appropriate prostanoids, comparing the said prostanoids with a control and determining oxidative stress on said comparison is conventional and within the skill of the art to which this invention pertains.

Applicants have argued that one could not extrapolate in vitro data to the in vivo efficacy. This may be true. However, Applicants are reminded that usually in vitro data or assays are used in screening procedures for potentially useful therapeutic agents in vivo. Further, the in vitro data contained in the Morrow et al. reference does indeed disclose or suggest the present invention to one of ordinary skill in the art because one of ordinary skill in the art would have been motivated to develop or use the already established in vitro data of the reference for the in vivo efficacy of the instantly claimed invention for the reasons discussed above.

With respect to Applicants allegation that there was nothing in the reference that suggested or taught any relevance of this chemistry to biological chemistry or biological process is not persuasive because it is the Examiner's position that the instantly claimed method and composition fall within the scope of the prior art method and composition and as such it would have been obvious for one of ordinary skill in the art to modify or optimize the "test-tube chemistry" since the general conditions

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of the claimed method and composition are disclosed in the prior art. Further, Applicants have acknowledged on page 2 of the Remarks (See the preliminary amendment filed 12/5/94) that the prior art teachings of in vitro has fulfilled a great need in the art which lead to the development of an assay to determine oxidative stress in vivo by the quantification of these prostaglandin compounds. Thus, one of skill in the art would have been motivated to correlate the in vitro data to potential animal model in order to determine the in vivo efficacy because, a person of ordinary skill in the art would know that a first line of experimentation is the "test-tube chemistry" (i.e. in vitro experimentation).

Applicants urge that the prior art of Morrow et al. was published in an "Analytical" Journal and the sole point of the article was to alert other scientists that prostaglandin can be generated during storage of biological samples. This is irrelevant, because whether the article is published in "Analytical" or "Biological" Journals is immaterial, what really matters is the content of the published material. In this case, the prior art clearly discloses an assay system based upon detection of multiple PGF₂ compounds with levels ranging from approximately 5 to 40 pg/m. Thus, motivating one of ordinary skill in the art to extrapolate the in vitro data to the in vivo

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efficacy because the expectation of success would have been viewed in the context of the entire prior art teachings.

With respect to 132 declaration of Dr. Marnett filed 12/5/94, the declaration has been considered but is not persuasive because (1) the declaration states on paragraph 4 that the discovery by the Applicants that prostaglandin F₂-like compounds were produced in vivo was surprising because it demonstrated that compounds related to prostaglandin could be formed chemically instead of enzymatically. However, the prior art of Morrow et al. (*Analytical Biochemistry*, Volume 184, pp. 1-10, 1990) clearly discloses the formation of PGF₂ compounds by nonenzymatic process, namely by chemical process (See the entire document and particularly the abstract, pages 5-6 and Figure 5).

(2) On paragraph 5, the declaration states that prior to Applicants' discovery there was no convincing evidence that free radical-catalyzed peroxidation of lipids actually occurred in vivo and Applicants were the first to provide the convincing evidence that peroxidation occurred in vivo. However, the reference of Morrow et al. states "in fact, we have obtained recent evidence suggesting that noncyclogenase formation of these compounds (PGF₂) is also occurring in vivo and that the levels reported here in fresh plasma appears to be formed endogenously" (See last paragraph of page 10). Thus, the prior art of Morrow et al. clearly showed that peroxidation occurred in vivo. In view of

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the above, the declaration is not persuasive. Accordingly, the declaration is insufficient to overcome the rejection of the pending claims under 35 USC 103.

With regard to Applicants allegation that before obviousness can be established, the Examiner must show that there is suggestion in the art to produce the claimed invention of a compelling motivation based on sound scientific principles is noted. However, it is the Examiner's position that in view of the implicit motivation of the analogous Morrow et al. in vitro data and as acknowledged by Applicants that the Morrow et al. reference lead to the Applicants investigating in this area further resulting in piquing Applicants curiosity (See page 29 of the brief filed 11/30/93 as Paper No. 16 on parent application Serial No. 07/715,419); the reference taken as a whole would have suggested Applicants invention of a method of determining oxidative stress in vivo by quantification of prostaglandin-like compounds and their metabolites produced by a noncyclooxygenase free radical catalyzed mechanism in either biological fluid or tissue and a composition thereof to one of ordinary skill in the art. Furthermore, obviousness does not require absolute predictability, In re Lamberti, 192 USPQ 278; In re Migel et al., 159 USPQ 716; In re Moreton, 129 USPQ 288 but only reasonable expectation of success, In re Longi, 225 USPQ 645; In re Pantzer et al., 144 USPQ 415; In re Farnham et al., 188 USPQ 365.

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Accordingly, it would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the teachings of Morrow et al., thus achieving the invention as a whole for the expected benefits of employing a method to determine oxidative stress in vivo by quantification of prostaglandin-like compounds and their metabolites produced by a noncyclooxygenase free radical catalyzed mechanism; absent of sufficient objective factual evidence or unexpected results to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 6:30 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Elizabeth C. Weimar, can be reached on (703) 308-0254. The fax phone number for this Group is (703) 305-3014.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C Weimar
ELIZABETH C. WEIMAR
SUPERVISORY PATENT EXAMINER
GROUP 1800

AAM Mohamed/AAM

May 28, 1996